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# Should Asymptomatic Ventricular Arrhythmias in Patients With Congestive Heart Failure Be Treated With Antiarrhythmic Drugs?

## I. Introduction

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Nearly 400,000 patients die of congestive heart failure each year. Although death may result from progressive left ventricular dysfunction or an intercurrent myocardial or cerebral ischemic event, nearly 35 to 45% of affected patients die suddenly, presumably as a consequence of a malignant ventricular tachyarrhythmia (1–3). Until recently, most pharmacologic approaches to the treatment of heart failure have been directed toward producing hemodynamic and symptomatic improvement, and there has been little effort directed at reducing sudden death.

*What can we do to ameliorate the problem of sudden death in patients with chronic heart failure?* Most patients with heart failure have complex yet asymptomatic ventricular arrhythmias (4–13). To the extent that such ambulatory arrhythmias are the predecessors of subsequent lethal events, we might be tempted to prevent sudden death by treating ventricular arrhythmias when they are detected during an asymptomatic phase. The advantages and disadvantages of treating such asymptomatic arrhythmias have become the focus of a lively and continuing debate.

**Prevalence of asymptomatic ventricular arrhythmias in heart failure (Table 1).** Studies using ambulatory electrocardiography indicate that 70 to 95% of patients with congestive heart failure secondary to ischemic heart disease or idiopathic dilated cardiomyopathy have frequent and complex ventricular premature beats, and that 40 to 80% have nonsustained ventricular tachycardia. Even a 4 h ambulatory recording, which was used in the Veterans Administration Vasodilator Heart Failure Trial (V-HeFT) (14), showed that 25 to 30% of patients with mild to moderate heart failure had asymptomatic nonsustained ventricular tachycardia. Long-term follow-up studies have also shown that 20 to 65% of patients with chronic heart failure die suddenly, the precise incidence being in part related to the definition of sudden death utilized in each report. Data from our own studies (1,15) (in which sudden death was defined as instantaneous death or death occurring during sleep) suggest that this devastating complication is equally distributed between patients with ischemic heart disease and idiopathic dilated cardiomyopathy. The frequency of sudden death is greater in patients with congestive heart failure than in any other definable group of patients with chronic heart disease and appears to be synergistically determined by the density and complexity of ventricular arrhythmias as well as the extent of left ventricular dysfunction.

**Predisposing factors to ventricular arrhythmias in heart failure.** Many factors appear to contribute to the occurrence of ventricular arrhythmias in patients with congestive heart failure. The fibrotic replacement of diseased or necrotic myocardium in this disorder may lead to the evolution of irritable foci and reentrant circuits. These electrophysiologic abnormalities may be exacerbated in individual patients by concurrent myocardial inflammation or ischemia. Mechanical factors (excessive left ventricular dilation and regional wall motion abnormalities) may also create unusual hemodynamic stresses that may contribute importantly to the pathogenesis of arrhythmias. Electrolyte imbalances, especially diuretic-induced potassium and magnesium depletion, are frequent in patients with congestive heart failure. Such deficits may interact in the presence of inotropic agents (digitalis, catecholamines and phosphodiesterase inhibitors) to provoke malignant ectopic rhythms. These observations have led some investigators (16) to suggest that the high circulating levels of catecholamines (and other neurohormones) that are found in patients with heart failure contribute importantly to the occurrence of fatal arrhythmias in this disorder. Although high levels of plasma norepinephrine are a poor prognostic finding (with respect to *total* mortality) in chronic heart failure (17), it is not clear that neurohormonal activation is an important cause of sudden death in these patients.

Because of the prevalence of ventricular arrhythmias, patients with congestive heart failure are commonly treated with antiarrhythmic drugs. Unfortunately, this therapeutic approach appears to be a frequent *cause* of serious arrhythmias in this disorder. Antiarrhythmic drugs may exacerbate arrhythmias in 5 to 20% of treated patients (18,19). Patients with chronic heart failure may be at particular risk of this complication, although such an association has not been carefully studied. Furthermore, the pharmacokinetics of many drugs, including antiarrhythmic agents, are greatly modified in patients with heart failure. Because most antiarrhythmic drugs have a narrow toxic/therapeutic ratio, this altered metabolic disposition may greatly complicate the safe and effective application of these agents. Finally, most



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Table 1. Prevalence of Complex Ventricular Arrhythmias in Congestive Heart Failure

| Study | Number of Patients | Couplets and Multiformed VPB (%) | Nonsustained VT (%) |
|---|---|---|---|
| Huang et al. (5) | 35 | 93 | 60 |
| Wilson et al. (7) | 77 | 71 | 50 |
| Meinertz et al. (9) | 74 | 87 | 49 |
| Maskin et al. (10) | 35 | 92 | 71 |
| Von Olshausen et al. (11) | 60 | 95 | 80 |
| Holmes et al. (12) | 31 | 87 | 39 |
| Chakko et al. (13) | 43 | 88 | 51 |
| V-HeFT* (20) | 346 | 81 | 28* |
| | 701 (total) | 87 (mean) | 54 (mean) |

*Preliminary results of the V-HeFT trial in which only 4 (rather than 24 h) recordings were performed. V-HeFT = Vasodilator Heart Failure Trial; VPB = ventricular premature beats; VT = ventricular tachycardia.

antiarrhythmic drugs can depress left ventricular function; this appears to be particularly true of drugs such as flecainide and disopyramide. These proarrhythmic and cardiodepressant effects of antiarrhythmic drugs have raised concerns that antiarrhythmic drugs may shorten survival and increase (rather than decrease) the occurrence of sudden death in patients with chronic heart failure. It is noteworthy in this regard that in the V-HeFT trial (20), the use of antiarrhythmic agents was an independent risk factor for shortened survival. However, because the use of antiarrhythmic drugs was not controlled in this study, it is difficult to determine if this association was observed because antiarrhythmic drugs were prescribed to high risk patients or because these agents contributed directly to the high mortality rate in this disease.

**Therapeutic considerations.** Until large, randomized trials are conducted to evaluate the effect of antiarrhythmic drugs on the survival of patients with heart failure, we do not know whether this therapeutic approach should be utilized to prevent sudden death. Such trials are the only means of determining whether there is a true (or only apparent) relation between ventricular arrhythmias and sudden death in this disorder (3). Such studies can be carried out in one of two ways. One approach is to enroll all subsets of patients with chronic heart failure. However, there is little evidence that the empiric application of antiarrhythmic agents is beneficial in these patients (13). A second approach is to enroll only patients who are at high risk of sudden death. Unfortunately, it is not clear how such high risk patients would be selected. Electrophysiologic testing may offer some prognostic information in patients with symptomatic arrhythmias (21), but it seems to be of limited utility in patients with asymptomatic rhythm disturbances (22,23), particularly if their heart failure is the result of idiopathic dilated cardiomyopathy (21,24). Signal-averaged electrocardiography and exercise testing may contribute to the assessment of risk in some patients (25), but the accuracy of these tests in patients without coronary artery disease has not been evaluated (3). Until a valid (preferably noninvasive) marker of sudden death risk can be identified in patients with congestive heart failure, virtually all patients with this disorder must be considered to be at risk for sudden death (2), and hence a potential candidate for intervention trials designed to test the utility of antiarrhythmic drugs.

*What should the clinician do about ventricular arrhythmias in patients with chronic heart failure?* Some investigators have suggested that converting enzyme inhibitors may reduce the frequency of sudden death in these patients. Although converting enzyme inhibitors prolong life in patients with heart failure (26) and appear to reduce the frequency and complexity of ventricular arrhythmias (27,28), it is not clear that these drugs can reduce the occurrence of sudden death in this disorder, although much controversy persists concerning this issue (29). If converting enzyme inhibitors exert clinically important antiarrhythmic effects in patients with chronic heart failure, this action does not appear to be mediated by an inhibitory effect of these drugs on the sympathetic nervous system because long-term treatment with captopril and enalapril may not prevent the progressive rise in plasma norepinephrine levels that is expected to follow progression of the heart failure state (30).

*Some investigators have suggested that amiodarone may be the most effective approach* to the treatment of patients with heart failure who have serious (yet asymptomatic) arrhythmias. Small uncontrolled trials (25,31) have shown that amiodarone therapy produces a dramatic reduction in the frequency and complexity of ventricular arrhythmias in patients with chronic heart failure. Although amiodarone is currently reserved for the treatment of *symptomatic* life-threatening arrhythmias because of concerns about the drug's predilection to produce serious adverse reactions, such toxicity appear to be dose related, and small doses of the drug (200 mg/day, for example) may be sufficient to suppress the occurrence of ventricular arrhythmias without depressing ventricular function (32). Amiodarone may be the only antiarrhythmic agent currently available that (either alone or in combination with other agents) may prolong life in patients with chronic heart failure (31), but there are serious concerns about administering this potentially toxic drug to asymptomatic patients with this disease until the validity of treating asymptomatic arrhythmias can be demonstrated.

**Conclusions.** Should asymptomatic ventricular arrhythmias in patients with chronic heart failure be treated with antiarrhythmic drugs in an effort to prevent sudden death? This question will be debated by Kanu Chatterjee and Eric Prystowsky in the following articles. We hope that this interaction will lead to the planning and conduct of a large scale, controlled clinical trial designed to definitively address this issue.

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# II. Protagonist's Viewpoint

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The principal rationale for the use of antiarrhythmic drugs in patients with congestive heart failure is to prevent the occurrence of sudden death. Of the 2,066 deaths in patients with chronic heart failure reported in long-term survival studies (1–15), 997 deaths (46%) were classified as sudden, although the incidence rate varied from 4 to 86% depending on the definition of sudden death used. In our own series of